

Remarks

By way of this Preliminary Amendment, claims 1-8, 10, 11 and 13-21 are pending. Claims 9 and 12 have been canceled. Claims 4, 6, 7, 8 and 13-18 have been amended to put the claims in a format appropriate for U.S. prosecution. Claims 19-21 have been added to include material deleted from amended claims 6 and 18. No new matter has been added by way of these amendments.

More specifically, claim 4 has been amended to specify that it is dependent on claim 1. Claim 6 has been amended to specify that R¹, R², R³, R³⁶, R³⁷, R³⁸, R³⁹, R^{36'}, R^{37'}, R^{38'}, R^{39'}, X, Y and A are as defined in Claim 1. Additionally, claim 6 has been amended to remove phrases such as "if appropriate," "preferably," and "customary". Material deleted from Claim 6 has been rewritten in new claims 19 and 20. Claim 8 has been amended to add the recitation of a pharmaceutically acceptable carrier to the claim. Claims 13-18 have been amended to convert the Swiss-type use claim to the U.S. method of treatment format. Finally, claim 18 has been amended so that the claim contains the proper multiple dependent claim format in compliance with 37 C.F.R. § 1.75(c) and to separate the claim into two independent claims. Material deleted from claim 18 has been rewritten in independent form in new claim 21.

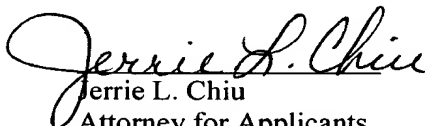
Conclusion

Applicants respectfully submit that the pending claims, as amended, are in condition for allowance. Please charge any fees due with this amendment to deposit account number 13-3372. If the Examiner believes that a conversation with Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned attorney at (203) 812-3964.

Respectfully submitted,

Dated: March 22, 2001

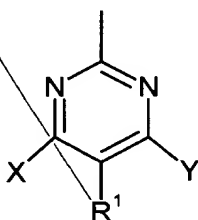
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4. (Amended) Compounds according to claim 1,

in which

R¹, X and Y are attached to the pyrimidine ring as follows



and

R¹ represents an optionally substituted cyclopropyl, cyclobutyl, cyclopentenyl, cyclopentyl, cyclohexyl, 1-hydroxycyclopropyl or 1-(fluoromethyl)cyclopropyl radical,

X represents NH₂

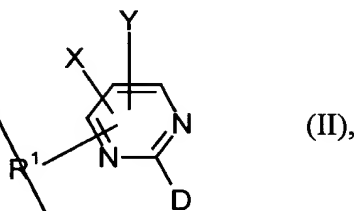
and

Y represents hydrogen or NH₂.

6. (Amended) Process for preparing the compounds of the general formula (I) according to Claim 1, characterized in that,

depending on the various meanings of the heterocycles listed above under R² and R³,

A²
Cont

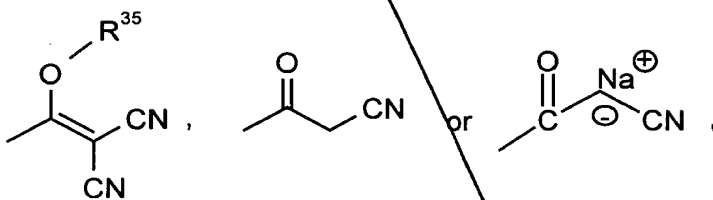


in which

R^1 , X and Y are each as defined above in claim 1,

and

D represents radicals of the formulae



in which

R³⁸ represents C₁-C₄-alkyl

are converted, by reaction with compounds of the general formula (III)

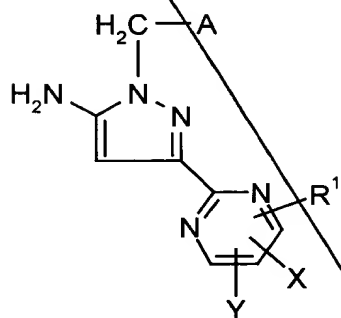


in which

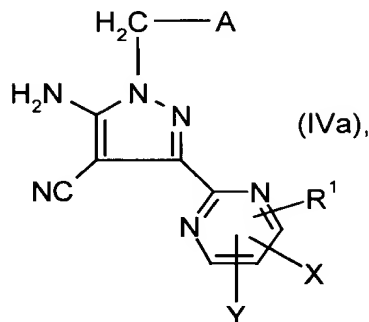
B' cont
A2 cont

A is as defined above in claim 1,

in inert solvents into the compounds of the general formula (IV) or (IVa)



(IV) and



in which

A, X, Y and R¹ are each as defined above in claim 1,

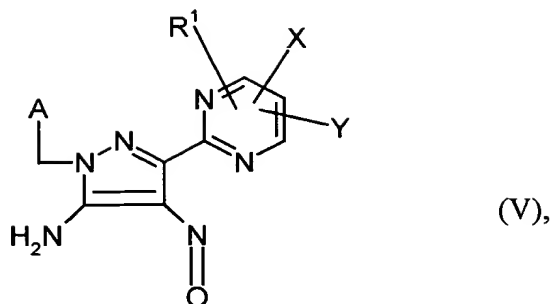
and, in the case of the compounds of the general formula (IVa), are subsequently cyclized with carboxylic acids, nitriles, formamides or guanidium salts,

and, in the case of the compounds of the general formula (IV), are cyclized with 1,3-dicarbonyl derivatives, their salts, tautomers, enol ethers or enamines, in the presence of acids,

or

[B] in the case that R² and R³ together form a pyrazine ring, compounds of the general formula (IV) are initially converted by nitrosation into the compounds of the general formula (V)

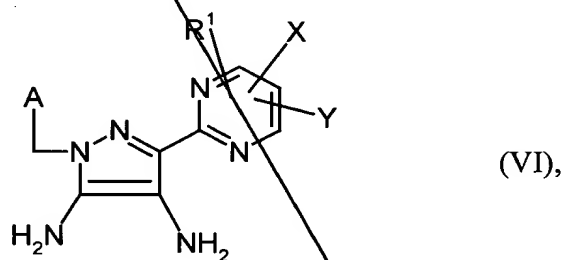
A2
Cont



in which

A, X, Y and R^1 are each as defined above in claim 1,

in a second step, the compounds of the general formula (VI)



in which

A, X, Y and R^1 are each as defined above in claim 1,

are prepared by a reduction,

and these are subsequently cyclized with 1,2-dicarbonyl compounds,

or

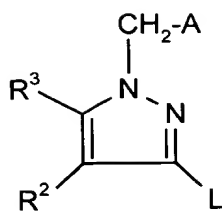
[C] compounds of the general formula (VII)

B¹
cont

A²

cont

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(VII),

in which

A^1 , R^2 and R^3 are each as defined above in claim 1,

and

L represents a radical of the formula $-\text{SnR}^{36}\text{R}^{37}\text{R}^{38}$, ZnR^{39} , iodine, bromine or triflate,

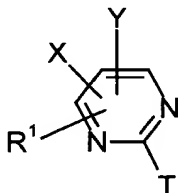
in which

R^{36} , R^{37} and R^{38} are identical or different and each represents straight-chain or branched alkyl having up to 4 carbon atoms

and

R^{39} represents halogen

are reacted with compounds of the general formula (VIII)



(VIII),

in which

X, Y and R¹ are each as defined above in claim 1,

and

in the case that L = SnR³⁶R³⁷R³⁸ or ZnR³⁹,

T represents triflate or represents halogen,

and,

in the case that L = iodine, bromine or triflate,

T represents a radical of the formula SnR^{36'}R^{37'}R^{38'}, ZnR^{39'} or BR^{40'}R^{41'},

in which

R^{36'}, R^{37'}, R^{38'} and R^{39'} have the meanings of R³⁶, R³⁷, R³⁸ and R³⁹ given above in claim 1 and are identical to or different from them,

R⁴⁰ and R⁴¹ are identical or different and each represent hydroxyl, aryloxy having 6 to 10 carbon atoms or straight-chain or branched alkyl or alkoxy having in each case up to 5 carbon atoms, or together form a 5- or 6-membered carbocyclic ring

in a palladium-catalysed reaction in inert solvents,

or

[D] amidines of the general formula (IX)

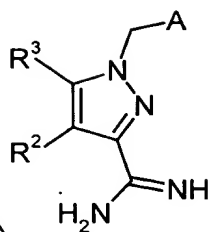
B1
cont

A2
cont

continued

B'
cont

A2
cont

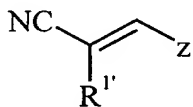


(IX),

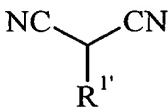
in which

A, R² and R³ are each as defined above in claim 1,

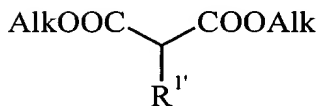
are reacted with compounds of the general formula (X), (Xa), (Xb) or (Xc)



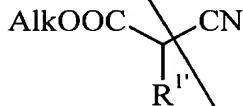
(X)



(Xa)



(Xb)



(Xc) ,

in which

R^{1'} represents the optionally substituted cycloalkyl radical listed above under R¹;

Alk represents straight-chain or branched alkyl having up to 8 carbon atoms,

and

~~Z represents an NH₂ group, a monoalkylamino group having up to 7 carbon atoms, a dialkylamino group having up to 7 carbon atoms, a piperidinyl or morpholinyl radical which is attached via the nitrogen, hydroxyl, alkoxy having up to 7 carbon atoms, acyloxy having up to 7 carbon atoms or aroyloxy having 6 to 10 carbon atoms,~~

C2
cont

8. (Amended) Medicaments, comprising at least one compound of the general formula (I) according to Claim 1 and a pharmaceutically acceptable carrier.

14. (Amended) The method of claim 13, wherein said cardiovascular disease is hypertension.

15. (Amended) A method of treating thromboembolic disorders and ischaemia, comprising administering to a mammal an effective amount of a compound according to claim 1.

16. (Amended) A method of treating sexual dysfunction, comprising administering to a mammal an effective amount of a compound according to claim 1.

17. (Amended) A method of treating inflammation, comprising administering to a mammal an effective amount of a compound according to claim 1.

A³

Cont

Q2

cont

18.

(Amended)

~~The method of claim 13, 14, 15, 16 or 17, wherein said compound of the general formula (I) according to Claim 1 is administered in combination with an organic nitrate or NO donor.~~

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C²
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A4

19. (New) The process of claim 6, wherein said compound of the general formula (IV) further are cyclized with 1,3-dicarbonyl derivatives, their salts, tautomers, enol ethers or enamines in the presence of acids under microwave irradiation.
20. (New) The process of claim 6, wherein said 1,2-dicarbonyl compound is aqueous glyoxal solution.
21. (New) The method of claim 13, 14, 15, 16 or 17, wherein said compound of the general formula (I) according to Claim 1 is administered in combination with a compound that inhibits the degradation of cyclic guanosine monophosphate (cGMP).

C²
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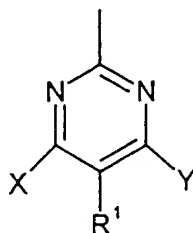
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Claim 1

4. Compounds according to ~~any of the preceding claims,~~

in which

- 5 R¹, X and Y are attached to the pyrimidine ring as follows



and

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R¹ represents an optionally substituted cyclopropyl, cyclobutyl, cyclopentenyl, cyclopentyl, cyclohexyl, 1-hydroxycyclopropyl or 1-(fluoromethyl)cyclopropyl radical,

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X represents NH₂

and

Y represents hydrogen or NH₂.

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5. Compounds according to claim 4, in which R¹ represents an optionally substituted cyclopropyl radical.

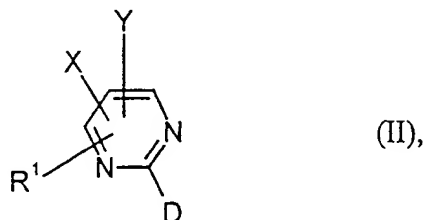
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6. Process for preparing the compounds of the general formula (I) according to Claim 1, characterized in that,

depending on the various meanings of the heterocycles listed above under R^2 and R^3 ,

[A] compounds of the general formula (II)

5



in which

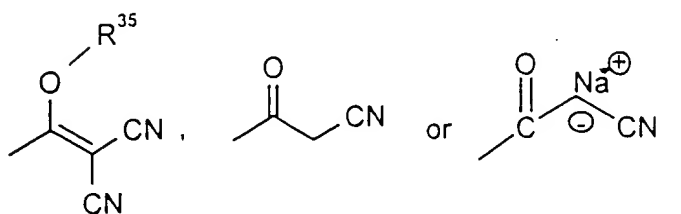
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R^1 , X and Y are each as defined above *in Claim 1*,

and

D represents radicals of the formulae

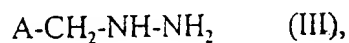
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R^{38} represents C_1 - C_4 -alkyl

are converted, by reaction with compounds of the general formula (III)

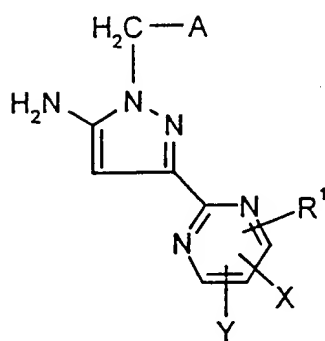


in which

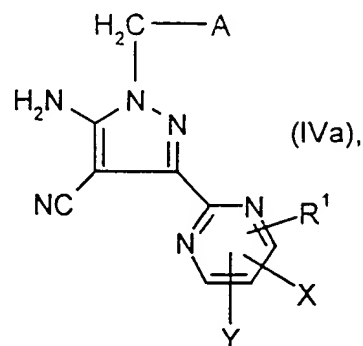
A is as defined above *in Claim 1,*

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in inert solvents, ~~if appropriate in the presence of a base,~~ into the compounds of the general formula (IV) or (IVa)



(IV) and



10

in which

A, X, Y and R¹ are each as defined above,

in Claim 1

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and, in the case of the compounds of the general formula (IVa), are subsequently cyclized with carboxylic acids, nitriles, formamides or guanidium salts,

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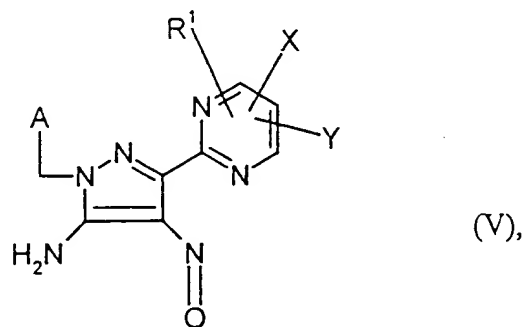
and, in the case of the compounds of the general formula (IV), are cyclized with 1,3-dicarbonyl derivatives, their salts, tautomers, ~~enol ethers or enamines, in the presence of acids and, if appropriate, under microwave irradiation,~~

or

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[B] in the case that R^2 and R^3 together form a pyrazine ring, compounds of the general formula (IV) are initially converted by nitrosation into the compounds of the general formula (V)

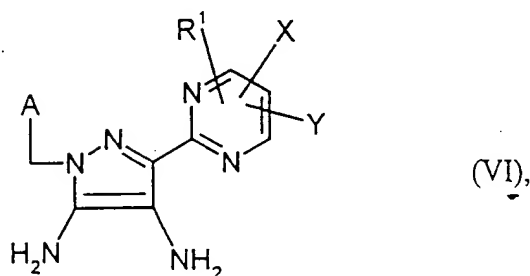


in which

A, X, Y and R^1 are each as defined above

in Claim 1

in a second step, the compounds of the general formula (VI)



in which

A, X, Y and R^1 are each as defined above

in Claim 1,

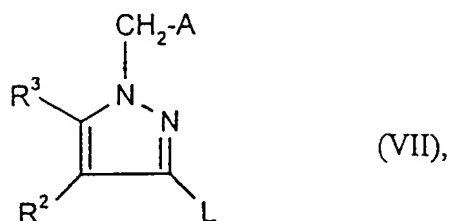
are prepared by a reduction,

and these are subsequently cyclized with 1,2-dicarbonyl compounds, preferably

~~aqueous glyoxal solution,~~

or

[C] compounds of the general formula (VII)



5

in which

A¹, R² and R³ are each as defined above *in Claim 1*,

10

and

L represents a radical of the formula -SnR³⁶R³⁷R³⁸, ZnR³⁹, iodine, bromine or triflate,

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in which

R³⁶, R³⁷ and R³⁸ are identical or different and each represents straight-chain or branched alkyl having up to 4 carbon atoms

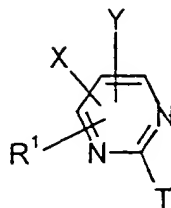
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and

R³⁹ represents halogen

are reacted with compounds of the general formula (VIII)

25



(VIII),

in which

X, Y and R¹ are each as defined above *in Claim 1,*

5

and

in the case that L = SnR³⁶R³⁷R³⁸ or ZnR³⁹,

10

T represents triflate or represents halogen, ~~preferably bromine~~

and,

in the case that L = iodine, bromine or triflate,

15

T represents a radical of the formula SnR³⁶R³⁷R³⁸, ZnR³⁹ or BR⁴⁰R⁴¹,

in which

20

R³⁶, R³⁷, R³⁸ and R³⁹ have the meanings of R³⁶, R³⁷, R³⁸ and R³⁹ given above and
are identical to or different from them, *in Claim 1*

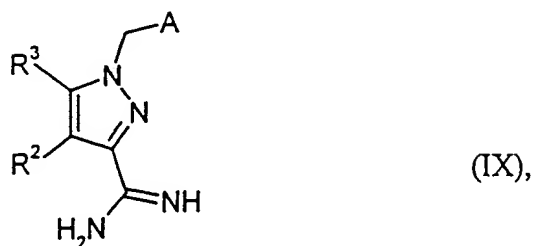
R⁴⁰ and R⁴¹ are identical or different and each represent hydroxyl, aryloxy
having 6 to 10 carbon atoms or straight-chain or branched alkyl or alkoxy
having in each case up to 5 carbon atoms, or together form a 5- or
6-membered carbocyclic ring

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in a palladium-catalysed reaction in inert solvents, ~~if appropriate in the presence~~
~~of a base,~~

or

5 [D] amidines of the general formula (IX)



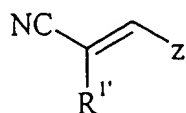
in which

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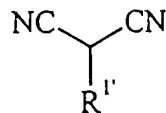
A, R² and R³ are each as defined above *in Claim 1,*

are reacted ~~for example,~~ with compounds of the general formula (X), (Xa),
 (Xb) or (Xc)

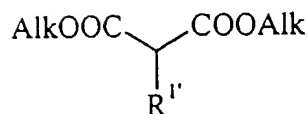
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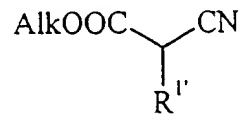
(X)



(Xa)



(Xb)



(Xc)

in which

R¹ represents the optionally substituted cycloalkyl radical listed above under R¹;

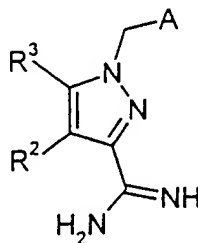
Alk represents straight-chain or branched alkyl having up to 8 carbon atoms, preferably up to four carbon atoms;

and

Z represents an NH₂ group, a monoalkylamino group having up to 7 carbon atoms, a dialkylamino group having up to 7 carbon atoms, a piperidinyl or morpholinyl radical which is attached via the nitrogen, hydroxyl, alkoxy having up to 7 carbon atoms, acyloxy having up to 7 carbon atoms or aryloxy having 6 to 10 carbon atoms,

and, if appropriate, the substituents listed under X, Y, R¹, R², R³ and/or A are modified or introduced by customary methods, preferably by acylation and derivatization of free amino groups, chlorination, catalytic hydrogenation, reduction, oxidation, removal of protective groups and/or nucleophilic substitution.

7. Amidines of the general formula (IX)



(IX),

in which

R², R³ and A are each as defined in one of the preceding Claims 1 to 3.

and their isomeric forms and salts.

8. Medicaments, comprising at least one compound of the general formula (I) according to Claim 1, *& a pharmaceutically acceptable carrier*
9. ~~Process for preparing medicaments, characterized in that at least one compound of the formula (I) according to Claim 1, if appropriate with customary auxiliaries and additives, is converted into a suitable administration form.~~ *canceled*
10. Medicaments, comprising at least one compound of the general formula (I) according to Claim 1 in combination with organic nitrates or NO donors.
11. Medicaments, comprising at least one compound of the general formula (I) according to Claim 1 in combination with compounds which inhibit the degradation of cyclic guanosine monophosphate (cGMP).
12. ~~Use of compounds of the general formula (I) according to Claim 1 for preparing medicaments.~~ *canceled*
13. *A method of treating a*
~~Use of compounds of the general formula (I) according to Claim 1 for preparing medicaments for the treatment of cardiovascular diseases,~~ *comprising administering to a mammal an effective amount of a compound according to Claim 1.*
14. ~~Use of compounds of the general formula (I) according to Claim 1 for preparing medicaments for the treatment of hypertension.~~ *The method of Claim 13, wherein said cardiovascular disease is*
15. ~~Use of compounds of the general formula (I) according to Claim 1 for preparing medicaments for the treatment of thromboembolic disorders and ischaemia.~~ *A method of treating comprising administering to a mammal an effective amount of a compound according to Claim 1*
16. ~~Use of compounds of the general formula (I) according to Claim 1 for preparing medicaments for the treatment of sexual dysfunction.~~ *A method of treating*

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- A method of treating inflammation, comprising*
17. ~~Use of compounds of the general formula (I) according to Claim 1 for administering to a mammal an effective amount of a compound according to Claim 1.~~
preparing medicaments having anti-inflammatory properties.
 - 5 18. ~~The method of~~ *13, 14, 15, 16 or 17*
~~Use according to any of Claims 12 to 17 where the compounds of the general formula (I) according to Claim 1 are used in combination with organic nitrates or NO donors or in combination with compounds which inhibit the degradation of cyclic guanosine monophosphate (cGMP).~~
in said
is administered an

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